December 16, 2025

Fujirebio Diagnostics,Inc.
Kristin Maddaloni
Senior Regulatory Affairs Specialist
201 Great Valley Pkwy.
Malvern, Pennsylvania 19475

Re: K250925
Trade/Device Name: ADVIA Centaur Cytokeratin Fragment 21-1
Regulation Number: 21 CFR 866.6010
Regulation Name: Tumor-Associated Antigen Immunological Test System
Regulatory Class: Class II
Product Code: OVK
Dated: March 27, 2025
Received: March 27, 2025

Dear Kristin Maddaloni:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-

assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Ying Mao -S

Ying Mao, Ph.D.
Branch Chief
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 07/31/2026
See PRA Statement below.

510(k) Number *(if known)*
K250925

Device Name
ADVIA Centaur Cytokeratin Fragment 21-1

Indications for Use *(Describe)*
The ADVIA Centaur Cytokeratin Fragment 21-1 (CYFRA) assay is for in vitro diagnostic use in the quantitative measurement of cytokeratin 19 fragments in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur XPT system.

The measurement of cytokeratin 19 is used as an aid in monitoring disease progression during the course of disease and treatment in lung cancer patients. Serial testing for patient CYFRA 21-1 assay values should be used in conjunction with other clinical information used for monitoring lung cancer.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

A. 510(k) Number:

K250925

B. Purpose for Submission:

New device

C. Measurand:

CYFRA 21-1

D. Type of Test:

Quantitative assay, automated sandwich immunoassay using acridinium ester chemiluminescent technology

E. Applicant:

Address: Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355

Contact person: Kristin Maddaloni
(484) 395-2126
maddalonik@fdi.com

F. Proprietary and Established Names:

ADVIA Centaur Cytokeratin Fragment 21-1 (CYFRA)

G. Regulatory Information:

1. Regulation section:
   21 CFR § 866.6010, Tumor-associated antigen immunological test system

2. Classification:
   Class II

3. Product code:
   OVK

4. Panel:
   Immunology

H. Intended Use:

1. Intended use(s):
   See indications for use below.

2. Indication(s) for use:
   The ADVIA Centaur® Cytokeratin Fragment 21-1 (CYFRA) assay is for in vitro diagnostic use in the quantitative measurement of cytokeratin 19 fragments in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur® XPT system.

   The measurement of cytokeratin 19 is used as an aid in monitoring disease progression during the course of disease and treatment in lung cancer patients. Serial testing for patient CYFRA 21-1 assay values should be used in conjunction with other clinical information used for monitoring lung cancer.

I. Special Conditions for Use Statement(s:)

For in vitro diagnostics use only.
Rx ONLY

J. Special Instrument requirements:

ADVIA Centaur XPT System (cleared under K141999)

K. Device Description:

The ADVIA Centaur® Cytokeratin Fragment 21-1 assay includes 1 ReadyPack primary reagent pack containing ADVIA Centaur CYFRA Lite Reagent and Solid Phase and ADVIA Centaur CYFRA master curve card.

The ReadyPack consists of the following:
ADVIA Centaur Cytokeratin Fragment 21-1 ReadyPack® primary reagent pack; Liquid Lite Reagent 10.0 mL/reagent pack KS19.1 monoclonal antibody acridinium conjugate in buffer containing bovine serum albumin; surfactant; and preservatives.
ADVIA Centaur Cytokeratin Fragment 21-1 ReadyPack® primary reagent pack; Liquid Solid Phase Reagent 17.5 mL/reagent pack BM19.21 monoclonal antibody coupled to magnetic microparticle bead in buffer containing bovine serum albumin; surfactant; and preservatives.

ADVIA Centaur Multi-Diluent13 ReadyPack ancillary reagent pack; 2×10.0mL/reagent pack; Buffer; surfactant; sodium azide (< 0.1%)

This assay is a fully automated 1-step sandwich immunoassay using acridinium ester chemiluminescent technology. The Solid Phase contains magnetic microparticles coated with anti-CYFRA 21-1 BM19.21 mouse monoclonal antibody. The Lite Reagent consists of acridinium ester-labeled anti-CYFRA 21-1 KS19.1 mouse monoclonal antibody. A direct relationship exists between the amount of CYFRA 21-1 present in the patient sample and the amount of relative light units (RLUs) detected by the system.

L. Substantial Equivalence Information:

1. Predicate device name(s):
   Elecsys CYFRA 21-1

2. Predicate 510(k) number(s):
   K160915

3. Comparison with predicate (reagents):

Similarities		
	ADVIA Centaur Cytokeratin Fragment 21-1 (Proposed Device)	**Elecsys CYFRA 21-1 (Predicate Device) K160915**
Device Type	*In vitro* diagnostic	Same
Classification	Class II	Same
CFR section	866.6010	Same
Product Code	OVK	Same
Product Usage	Clinical and Hospital laboratories	Same
Intended Use	The ADVIA Centaur® Cytokeratin Fragment 21-1 (CYFRA) assay is for in vitro diagnostic use in the quantitative measurement of cytokeratin 19 fragments in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur® XPT system. The measurement of cytokeratin 19 is used as an aid in monitoring disease progression during the course of disease and treatment in lung cancer patients. Serial testing for patient CYFRA 21-1 assay values should be used in conjunction with other clinical information used for monitoring lung cancer.	The CYFRA 21-1 EIA kit is intended for the quantitative determination of soluble cytokeratin 19 fragments in human serum. The assay is to be used as an aid in monitoring disease progression during the course of disease and treatment in lung cancer patients. Serial testing for patient CYFRA 21-1 assay values should be used in conjunction with other clinical methods used for monitoring lung cancer.
Specimen Collection Method	Routine Phlebotomy Techniques	Same
Analyte	CYFRA 21-1	Same

Differences		
	ADVIA Centaur Cytokeratin Fragment 21-1 (Proposed Device)	**Elecsys CYFRA 21-1 (Predicate Device) K160915**
Instrument System	ADVIA Centaur	Cobas e immunoassay analyzer
Principle of Operation	Sandwich immunoassay using acridinium ester chemiluminescent technology	Electrochemiluminescence immunoassay (ECLIA)
Type of Specimen	Serum, EDTA plasma, lithium heparin plasma	Human serum and plasma
Measuring Interval	0.49 – 100.00 ng/mL (0.49 - 100.00 µg/L)	0.1-500 ng/mL
Interpretation of Results	Master Curve	Calibration Curve and master curve

4. Comparison with predicate (calibrators):

Similarities		
	ADVIA Centaur Cytokeratin Fragment 21-1 Calibrator (CYFRA CAL) (Proposed Device)	**Elecsys CYFRA 21-1 CalSet (Predicate Device) K160915**
Intended Use	The ADVIA Centaur® Cytokeratin Fragment 21-1 Calibrator (CYFRA CAL) is for *in vitro* diagnostic use in calibrating the ADVIA Centaur® Cytokeratin Fragment 21-1 assay using the ADVIA Centaur® systems.	CYFRA 21-1 CalSet is used for calibrating the quantitative Elecsys CYFRA 21-1 assay on the Elecsys and cobas e immunoassay analyzers.
Levels	Two	Same
Stability - Unopened	2-8°C until expiration date on product	Same

Differences		
	ADVIA Centaur Cytokeratin Fragment 21-1 Calibrator (CYFRA CAL) (Proposed Device)	**Elecsys CYFRA 21-1 CalSet (Predicate Device) K160915**
Matrix	Bovine serum	Human Serum
Antigen Source	Cytokeratin 8/19 antigen	Cytokeratin from cell culture of the cell line MCF-7
Format	Liquid	Lyohpilized
Stability Opened/On-Board	Opened: At room temperature- 5 hours	On board: 20–25°C - up to five hours
Stability - Reconstituted	N/A	2–8°C: seven days −15 to −25°C: eight weeks (freeze only once)
Handling	Calibrators are liquid and ready to use. Allow materials to equilibrate to room temperature. Gently mix and invert the vials to ensure homogeneity of the material.	Add exactly 1.0 mL of distilled water and allow to stand closed for 15 minutes to reconstitute.

5. Comparison with predicate (controls):

Similarities		
	ADVIA Centaur Tumor Marker Quality Control (TM QC) (Proposed Device)	**PreciControl Tumor Marker (Predicate Device) K160915**
Intended Use	The ADVIA Centaur Tumor Marker Quality Control (TM QC) is for in vitro diagnostic use in monitoring the precision and accuracy of the ADVIA Centaur Tumor Marker assays using an ADVIA Centaur system.	PreciControl Tumor Marker is used for quality control of Elecsys immunoassays on Elecsys and cobas e immunoassay analyzers.
Stability - Unopened	2-8°C until expiration date on product	Same
Format	Lyophilized	Same
Matrix	Human serum	Same
Levels	Two	Same

Differences		
	ADVIA Centaur Tumor Marker Quality Control (TM QC) (Proposed Device)	**PreciControl Tumor Marker (Predicate Device) K160915**
Handling	1.) Reconstitute the controls by adding exactly 3.0 mL distilled or deionized water to each lyophilized control. 2.) Replace the control vial stopper. 3.) Let the control vials stand at room temperature for 15 minutes. Occasionally swirl. Do not mix by inversion. 4.) Mix the controls by vortexing for 2 to 3 seconds until controls are homogenous.	Add exactly 1.0mL of distilled water and allow to stand closed for 30 minutes to reconstitute.
Stability – On Board	On the system at room temperature for 5 hours	On-board 20–25°C: five hours
Analyte	SCCA1, CYFRA 21-1, NSE (Human), and ProGRP	AFP, CEA, CA 15-3 II, CA 125 II, Ferritin, tPSA, fPSA, CA 19-9, CYFRA 21-1
Stability - Reconstituted	2-8°C for 7 days; ≤ -20°C for 30 days - thaw only once	2–8°C: 14 days −15 to −25°C: four weeks 20–25°C: 24 hours

M. Standard/Guidance Document Referenced (if applicable):

- CLSI EP05-A3 (Reaffirmed: September 2019) Recognition # 7-251
- CLSI EP06 2nd Edition Recognition # 7-306
- CLSI EP17-A2 Recognition # 7-233
- CLSI EP07 3rd Edition Recognition # 7-275
- CLSI EP37 1st Edition Recognition # 7-284
- CLSI EP34 1st Edition Recognition # 7-290
- CLSI EP28-A3 (Formerly C28-A3c) Recognition # 7-224
- CLSI EP35 1st Edition Recognition # 7-298
- CLSI EP39 1st Edition Recognition #7-311
- CLSI EP09c 3rd Edition Recognition #7-296
- CLSI EP21 2nd Edition (Replaces EP21-A) Recognition #7-268
- CLSI EP25-A (Replaces EP25-P) Recognition # 7-235

N. Test Principle:

This assay is a fully automated sandwich immunoassay using acridinium ester chemiluminescent technology. The assay employs two anti-CYFRA 21-1 antibodies. The first antibody in the Lite Reagent, is a mouse monoclonal anti-CYFRA 21-1 (KS19.1) labeled with acridinium ester. The second antibody is a mouse monoclonal anti- CYFRA 21-1 (BM19.21) covalently coupled to paramagnetic microparticles in the Solid Phase. A direct relationship exists between the amount of CYFRA 21-1 present in the patient sample and the amount of relative light units (RLUs) detected by the system.

O. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*

      Precision was determined using the ADVIA Centaur XPT system in accordance with CLSI Document EP05-A3. Samples were assayed in replicates of 2 with 2 runs per day using a 20-day protocol. The following results are representative of the performance of the assay:

			Repeatability		Within-Laboratory Precision	
Sample	N[a]	Mean ng/mL (µg/L)	SD[b] ng/mL (µg/L)	CV[c] (%)	SD ng/mL (µg/L)	CV (%)
Serum A	80	2.03	0.03	N/A[d]	0.04	N/A
Serum B	80	2.84	0.03	N/A	0.06	N/A
Serum C	80	4.69	0.06	1.3	0.09	1.9
Serum D	80	15.15	0.24	1.6	0.31	2.1
Serum E	80	25.30	0.36	1.4	0.44	1.7
Serum F	80	65.46	0.80	1.2	1.09	1.7
Serum G	80	84.07	1.03	1.2	1.46	1.7

a Number of measurements
b Standard deviation
c Coefficient of variation
d Not applicable.

Reproducibility was determined using the ADVIA Centaur XPT system in accordance with CLSI Document EP05-A3. Testing was performed using 3 sites and 1 reagent lot. Samples were assayed in replicates of 3 with 2 run(s) per day using a 5-day protocol (Number of measurements per sample = 90). The following results are representative of the performance of the assay:

		Repeatability		Between Run		Between Day		Between Site		Reproducibility	
Sample	Mean ng/mL (µg/L)	SD[a] ng/mL (µg/L)	CV[b] (%)	SD ng/mL (µg/L)	CV (%)	SD ng/mL (µg/L)	CV (%)	SD ng/mL (µg/L)	CV (%)	SD ng/mL (µg/L)	CV (%)
Serum A	1.95	0.04	N/A[c]	0.01	N/A	0.03	N/A	0.07	N/A	0.09	N/A
Serum B	2.76	0.05	N/A	0.05	N/A	0.00	N/A	0.04	N/A	0.08	N/A
Serum C	4.65	0.08	1.6	0.07	1.6	0.06	1.3	0.00	0.0	0.12	2.6
Serum D	15.23	0.28	1.8	0.11	0.7	0.11	0.7	0.39	2.6	0.50	3.3
Serum E	25.48	0.50	2.0	0.19	0.7	0.23	0.9	0.44	1.7	0.73	2.9
Serum F	65.84	1.09	1.7	0.33	0.5	0.85	1.3	0.44	0.7	1.48	2.3
Serum G	84.18	1.38	1.6	0.00	0.0	1.13	1.3	1.14	1.4	2.11	2.5

a Standard deviation
b Coefficient of variation
c Not applicable

b. Linearity/assay reportable range:

Linearity testing was performed using the ADVIA Centaur XPT system in accordance with CLSI Document EP06-ed2. The assay is linear for the measuring interval of 0.49-100.00 ng/mL (0.49-100.00 µg/L).

c. *High Dose Hook Effect:*
High CYFRA 21-1 concentrations can cause a paradoxical decrease in the RLUs (high-dose hook effect). In this assay, no hook effect was observed up to 2500 ng/mL (2500 µg/L).

d. *Measuring Interval:*
0.49 – 100.00 ng/mL (0.49 - 100.00 µg/L)
The lower limit of the measuring interval is defined by the limit of quantitation (LoQ).
Report results below the measuring interval as < 0.49 ng/mL (0.49 µg/L).

e. *Detection limit:*
Detection capability was determined in accordance with CLSI Document EP17-A2. Results obtained at individual laboratories may vary from the data presented.

Detection Capability	Result
Limit of Blank (LoB)	0.48 ng/mL (µg/L)
Limit of Detection (LoD)	0.49 ng/mL (µg/L)
Limit of Quantitation (LoQ)	0.49 ng/mL (µg/L)

The LoB corresponds to the highest measurement result likely to be observed for a blank sample with a probability of 95%.

The LoD corresponds to the lowest analyte concentration that can be detected with a probability of 95%.

The LoQ corresponds to the lowest analyte concentration at which the within laboratory CV is ≤ 20%.

f. *Analytical specificity:*

Hemolysis, Icterus, Lipemia (HIL)

Interference testing was performed using the ADVIA Centaur XPT system in accordance with CLSI Document EP07-ed3 and EP37-ed1. Clinically significant interference as defined by bias greater than 10% was not observed for the following substances when tested at analyte concentrations of approximately 3.30 ng/mL (3.30 µg/L) and 25.00 ng/mL (25.00 µg/L).

Substance	Substance Test Concentration
Hemoglobin	1500 mg/dL (15 g/L)
Bilirubin, conjugated	66 mg/dL (783 µmol/L)
Bilirubin, unconjugated	66 mg/dL (1129 µmol/L)
Lipemia (Intralipid)	1500 mg/dL (15 g/L)

Other Substances

Interference testing was performed using the ADVIA Centaur XPT system in accordance with CLSI Document EP07-ed3 and EP37-ed1. Clinically significant interference as defined by bias greater than 10% was not observed for the following substances when tested at analyte concentrations of approximately 3.30 ng/mL (3.30 µg/L) and 25.00 ng/mL (25.00 µg/L).

Substance	Substance Test Concentration	Substance	Substance Test Concentration
5-Fluorouracil	500 µg/mL (3844 µmol/L)	Heparin	5000 U/L
Acetaminophen	200 µg/mL (1323 µmol/L)	Ibuprofen	500 µg/mL (2424 µmol/L)
Acetylcysteine	553 µg/mL (3389 µmol/L)	Leucovorin	750 µg/mL (1466 µmol/L)
Acetylsalicylic Acid	1000 µg/mL (5551 µmol/L)	Levodopa	20 µg/mL (101 µmol/L)
Ampicillin-Na	1000 µg/mL (2693 µmol/L)	Melphalan	15 µg/mL (49 µmol/L)
Ascorbic Acid	300 µg/mL (1703 µmol/L)	Methotrexate	1000 µg/mL (2201 µmol/L)
Bevacizumab	750 µg/mL	Methyldopa	20 µg/mL (84 µmol/L)
Biotin	3500 ng/mL (14 µmol/L)	Metronidazole	200 µg/mL (1169 µmol/L)
Carboplatin	1000 µg/mL (2694 µmol/L)	Mitomycin	25 µg/mL (75 µmol/L)
Cefoxitin	2500 µg/mL (5563 µmol/L)	Nivolumab	225 µg/mL
Chyle	3000 mg/dL (33.87 mmol/L)	Paclitaxel	265 µg/mL (310 µmol/L)
Cisplatin	45 µg/mL (150 µmol/L)	Pembrolizumab	150 µg/mL
Clotrimazole	0.3 µg/mL (1 µmol/L)	Phenylbutazone	400 µg/mL (1297 µmol/L)
Cyclophosphamide	1000 µg/mL (3583 µmol/L)	Rheumatoid Factor	1200 IU/mL (3.24 g/L)
Cyclosporine	5 µg/mL (4 µmol/L)	Rifampicin	60 µg/mL (73 µmol/L)
Dexamethasone	20 µg/mL (51 µmol/L)	Rituximab	750 µg/mL
Doxorubicin	120 µg/mL (207 µmol/L)	Tamoxifen	50 µg/mL (135 µmol/L)
Doxycycline	50 µg/mL (97 µmol/L)	Tarceva	30 µg/mL (70 µmol/L)
Etoposide	400 µg/mL (680 µmol/L)	Theophylline	100 µg/mL (555 µmol/L)
Human Anti-Mouse Antibodies	805 µg/L (8.05 x 10^{-4} g/L)	Total Protein (Human Serum Albumin)	15 g/dL (150 g/L)

Cross Reactivity

Cross-reactivity was determined using the ADVIA Centaur XPT system in accordance with CLSI Document EP07-ed3. Cross-reactivity of samples spiked with various substances does not exceed 10% at analyte concentrations of approximately 3.30 ng/mL (3.30 µg/L) and 25.00 ng/mL (25.00 µg/L).

Substance	Substance Test Concentration	Substance	Substance Test Concentration
AFP	810 ng/mL (810 µg/L)	CA 15-3	550 U/mL (550 kU/L)
β-hCG	517 mIU/mL (47 µg/L)	CA 19-9	4167 U/mL (4167 kU/L)
CA 125	4000 U/mL (4000 kU/L)	CEA	500 ng/mL (500 µg/L)

2. Comparison studies:

a. Method Comparison

Assay comparison was determined with the weighted Deming regression model using the ADVIA Centaur XPT system in accordance with CLSI Document EP09c-ed3.
Agreement of the assays may vary depending on the study design, comparative assay, and population tested.
Sample: Serum
Comparative Assay (x): commercial CYFRA 21-1 assay
Regression Equation ng/mL (µg/L): y=0.98x-0.378
Sample Interval ng/mL (µg/L): 0.98 – 90.05
N: 115
r: 0.975

b. Specimen Equivalency

Specimen equivalency was determined with the weighted Deming regression model using the ADVIA Centaur XPT system in accordance with CLSI Document EP09c ed3. Agreement to the specimen typers may vary depending on the study design and population tested.

Tube (y) vs. Serum (x)	**Regression Equation ng/mL (µg/L)**	**Sample Interval ng/mL (µg/L)**	**N[a]**	**r[b]**
Gel-barrier tube (serum)	y = 1.01x – 0.01	0.80–79.10	61	1.00
Gel-barrier tube (lithium heparin plasma)	y = 1.00x + 0.02	0.82-83.53	61	1.00
Plasma, lithium heparin	y = 1.00x + 0.03	0.80-80.83	61	1.00
Plasma, dipotassium EDTA	y = 0.99x + 0.01	0.81-82.81	61	1.00
Plasma, tripotassium EDTA	y = 0.96x + 0.03	0.84-77.98	61	1.00

a Number of samples tested.
b Correlation coefficient

3. Clinical studies:

a. Clinical sensitivity:

See 3(c) below

b. Clinical specificity:

See 3(c) below

c. Other clinical supportive data (when a. and b. are not applicable):

Clinical Performance

The effectiveness of the ADVIA Centaur XPT CYFRA 21-1 assay as an aid in monitoring the course of disease in lung cancer patients was determined through a prospective clinical study. Changes in CYFRA 21-1 levels were assessed in serial serum samples from 93 patients compared to changes in disease status. A total of 462 samples were measured, including 93 initial draws and 369 longitudinal follow-up draws. The population was comprised of 77 non-small cell lung cancer subjects (83%) and 16 small cell lung cancer subjects (17%).

Subjects were prospectively enrolled and had ≥ 3 blood draws over time with no less than 7 days between consecutive blood draws. Disease progression was defined as an increase in CYFRA 21-1 value that was at least 50% greater than the previous value and above the 95% reference limit of 2.77 ng/mL for the assay. Sixteen (32%) of the samples with a positive change correlated with disease progression while 283 (89%) of the samples with no significant change in CYFRA21-1 value correlated with no progression (samples with a clinical status of responding, stable, or no evidence of disease). The following tables present the data:

Change in CYFRA 21-1 Concentration	No Progression	Progression	Total
< 50.0% Increase and Current CYFRA 21-1 Value > 2.77 ng/mL OR Current CYFRA 21-1 Value ≤ 2.77 ng/mL	283	36	319
≥ 50.0% Increase and Current CYFRA 21-1 Value > 2.77 ng/mL	34	16	50
Total	317	52	369

Measure	Value	Lower Confidence Interval	Upper Confidence Interval
Sensitivity	30.8%	19.6%	42.0%
Specificity	89.3%	85.9%	92.4%
Total Concordance	81.0%	76.9%	84.9%
Positive Predictive Value (PPV)	32.0%	21.7%	42.8%
Negative Predictive Value (NPV)	88.7%	87.1%	90.4%
Positive Likelihood Ratio (PLR)	2.87	1.69	4.56
Negative Likelihood Ratio (NLR)	0.78	0.65	0.91

No set cutoff exists for CYFRA 21-1. The clinical performance of other percent changes in serial samples and a current CYFRA 21-1 value of > 2.77 ng/mL are presented below. Clinicians may choose to use these other values to enhance the sensitivity or specificity of the assay, depending on their needs.

Percent (%) Change in CYFRA 21-1	Sensitivity (%)	Specificity (%)	Negative Predictive Value (%)	Positive Predictive Value (%)
≥ 30.0%	34.6	84.5	88.7	26.9
≥ 40.0%	34.6	86.4	89.0	29.5
≥ 50.0%	30.8	89.3	88.7	32.0
≥ 60.0%	28.8	90.9	88.6	34.1
≥ 70.0%	25.0	92.7	88.3	36.1

4. Expected values/Reference range:

A reference interval for healthy adults was established in accordance with CLSI Document EP28-A3c on the ADVIA Centaur XPT system.

Samples were collected prospectively from apparently healthy subjects, smokers and nonsmokers, female or male, 22 years of age or older. The reference interval was determined by calculating the 2.5th and 97.5th percentiles of the distribution of values. Apparently healthy CYFRA 21-1 values, for smokers and non-smokers, were determined to be ≤ 3.48 ng/mL and ≤ 2.77 ng/mL for non-smokers.

		Median	Reference Interval
Group	N[a]	ng/mL (µg/L)	ng/mL (µg/L)
Adults (22 - 87 years)	239	1.36	0.75 - 3.48
Smoker (22 - 71 years)	119	1.56	0.78 - 5.69
Non-Smoker (22 - 87 years)	120	1.22	0.71 - 2.77

a Number of samples tested

The distribution in percentage (%) of CYFRA 21-1 assay values in benign and malignant cohorts was determined using 868 serum samples obtained from 9 U.S-based clinical centers and commercially available sources using the ADVIA Centaur CYFRA 21-1 assay.

		Percentage > 2.77 ng/mL	Mean	SD	25th Percentile	Median	75th Percentile
Group	N[a]	(%)	ng/mL (µg/L)	ng/mL (µg/L)	ng/mL (µg/L)	ng/mL (µg/L)	ng/mL (µg/L)
Benign Conditions							
Breast diseases	40	2.5	1.26	0.53	0.92	1.11	1.38
Liver diseases	40	30.0	2.70	2.12	1.36	1.88	3.02

Group	N[a]	Percentage > 2.77 ng/mL (%)	Mean ng/mL (µg/L)	SD ng/mL (µg/L)	25th Percentile ng/mL (µg/L)	Median ng/mL (µg/L)	75th Percentile ng/mL (µg/L)
Lung diseases	75	17.3	2.05	1.76	1.32	1.71	2.16
Congestive heart failure	38	21.1	2.43	1.86	1.50	1.78	2.57
Renal diseases	40	45.0	4.41	8.65	1.90	2.54	3.59
Cancer							
Bladder	40	20.0	1.89	1.00	1.00	1.64	2.47
Breast	45	20.0	2.88	4.23	1.31	1.76	2.29
Cervical	39	20.5	2.67	4.64	1.04	1.38	2.19
Colorectal	40	42.5	6.72	13.23	1.89	2.51	3.65
Esophageal Squamous Cell	40	22.5	2.27	1.51	1.38	1.72	2.48
Head & Neck	39	43.6	5.68	9.47	1.74	2.45	4.99
Treatment-naïve NSCLC	119	47.9	7.48	19.11	1.62	2.59	5.89
Treatment-naïve SCLC	113	41.6	6.31	16.36	1.53	2.19	4.66
Ovarian	40	52.5	13.62	28.05	1.40	2.91	9.06
Prostate	40	30.0	4.32	12.31	1.50	2.29	3.01
Testicular	40	12.5	2.98	7.64	0.95	1.32	1.58
Stomach	40	25.0	6.87	17.91	1.44	1.68	2.79

a Number of samples tested.

P. Proposed Labeling:

The labeling supports the finding of substantial equivalence for the device.

Q. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.